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ORIGINAL ARTICLE

A study of the geographic distribution and associated risk factors of leg ulcers within an international cohort of sickle cell disease patients: the CASiRe group analysis

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Abstract

Vasculopathy is a hallmark of sickle cell disease ultimately resulting in chronic end organ damage. Leg ulcer is one of its sequelae, occurring in ~ 5–10% of adult sickle cell patients. The majority of leg ulcer publications to date have emanated from single center cohort studies. As such, there are limited studies on the geographic distribution of leg ulcers and associated risk factors worldwide. The Consortium for the Advancement of Sickle Cell Research (CASiRe) was formed to improve the understanding of the different phenotypes of sickle cell disease patients living in different geographic locations around the world (USA, UK, Italy, Ghana). This cross-sectional cohort sub-study of 659 sickle cell patients aimed to determine the geographic distribution and risk factors associated with leg ulcers. The prevalence of leg ulcers was 10.3% and was associated with older age, SS genotype, male gender, and Ghanaian origin. In fact, the highest prevalence (18.6%) was observed in Ghana. Albuminuria, proteinuria, increased markers of hemolysis (lower hemoglobin, higher total bilirubin), lower oxygen saturation, and lower body

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mass index were also associated with leg ulceration. Overall, our study identified a predominance of leg ulcers within male hemoglobin SS patients living in sub-Saharan Africa with renal dysfunction and increased hemolysis.

Keywords Leg ulcers · Sickle cell · Hemolysis · International

Introduction

Sickle cell disease (SCD) is a genetic blood disorder characterized by the sickling of red blood cells resulting in pain episodes and end organ damage with increased morbidity and mortality in affected patients [1, 2]. The sickled red blood cells eventually lead to vessel occlusion and tissue ischemia [2]. Complications including vaso-occlusive crises, splenic dysfunction, priapism, acute chest syndrome, kidney failure, pulmonary hypertension, osteonecrosis, retinopathy, and cerebrovascular disease are the clinical sequelae of ongoing SCD vasculopathy [3–5]. Additionally, leg ulcers are frequent and debilitating, particularly among those with the SS genotype [5, 6].

The first SCD patient described in the medical literature suffered from leg ulceration [7]. Such patients are at risk of developing other complications including priapism, renal disease, and pulmonary hypertension [4, 6, 8]. In fact, leg ulcers are frequently observed in SCD patients with pulmonary hypertension, suggesting a possible pathophysiologic relationship between these two complications [5, 6, 9]. Furthermore, both leg ulcers and pulmonary hypertension increase in prevalence with increasing age and are associated with lower levels of hemoglobin and higher levels of serum lactate dehydrogenase, both indicators of hemolysis [8, 10, 11].

Geographical location, SCD genotype, gender, as well as age were proposed as factors influencing the prevalence of leg ulceration in SCD patients in a previous study [6]. However, there are limited studies on the geographical distribution of leg ulcers and associated risk factors worldwide, with the majority being reported from single cohort studies. Previous studies have shown a high prevalence of leg ulcers in Jamaica (75%) as compared with North America (1–10%) and Saudi Arabia (1%) [6, 12–15]. Leg ulceration is also less common among SCD adults in Central India [16, 17] and the Eastern Province of Saudi Arabia [14], where patients typically have the Asian haplotype. Although the incidence of leg ulcers in SCD patients with SS genotype was found to be 9.97/100 persons in a US Cooperative Study of SCD [12], the actual global incidence of leg ulcers is not known. The merits of understanding and determining the possible risk factors for leg ulceration in SCD patients as well as the worldwide geographical distribution cannot be overstated, as it informs the preventative and control measures for effective management of this disease-related complication. The current study aimed to determine the geographical distribution and clinical and demographic risk factors associated with leg ulcers in an international cohort of SCD patients.

Methods

Participant recruitment and data collection

The Consortium for the Advancement of Sickle Cell Research (CASiRe) is an international, multi-institutional, collaborative group evaluating the clinical severity of adults and children with SCD through a validated questionnaire and medical chart review, standardized across 4 countries (USA, UK, Italy, and Ghana). The CASiRe consortium includes 6 sites in the USA (University of Michigan-Mott Children's Hospital, Rainbow Babies and Children's Hospital, Promedica Toledo Children's Hospital, Children's Hospital at Montefiore, Connecticut Children's Medical Center, University of Connecticut Health Center), 2 sites each in Ghana (Ghana Institute of Clinical Genetics, Korle Bu Teaching Hospital and Pediatric Sickle Cell Clinic at Korle Bu Teaching Hospital) and Italy (University of Campania Luigi Vanvitelli, Azienda Ospedaliera-Università di Padova, Italy), and a single site in the UK (Guys and St. Thomas Hospital).

While 877 patients have been enrolled to date, 659 subjects from the USA, Ghana, and Italy who reported on a history of leg ulcers (present or absent) were included in this analysis. Leg ulcer data from the UK site were not available. Between 2011 and 2017, after obtaining Institutional Review Board (IRB) approval at each site and written informed consent, demographic, clinical, and laboratory data were collected by interviewing the patient and/or parent/guardian as well as by medical chart abstraction. At the 2 sites (Guys and St Thomas Hospital, UK; Azienda Ospedaliera-Università di Padova, Italy) with existing IRB-approved SCD registries or standardized disease specific data collection, data were abstracted directly from their respective databases. Demographic data included age, race, gender, country of birth of patient, parents, and grandparents. Clinical data included vital signs, height, weight, body mass index (BMI), oxygen saturation (SatO2), leg ulcer history and other past medical history, past surgical history, family history, hydroxyurea use, and transfusion history. Laboratory markers including hematological, biochemical, and electrophoretic data were obtained from the medical chart. Leg ulcer (not necessarily active) was defined as a

defect in the skin beneath the knee and above the foot, which persisted for 6 or more weeks.

Data analysis

Descriptive statistical analyses including mean, range, standard deviation, and percentages were performed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0). We analyzed the frequency of leg ulcers and associated clinical and demographic risk factors. Results were expressed as mean plus or minus standard deviation (mean ± SD). Statistical significance was considered at $p < 0.05$.

Results

Demographic and clinical features of the study participants

A total of 659 subjects from the cohort had data evaluable in the medical history for the presence or absence of leg ulcers (Table 1). Among these subjects, 255 were from the USA, 318 were from Ghana, and 86 were from Italy (Table 1). A total of 68 patients (10.3%) reported a history of leg ulcers (Table 1). The prevalence of a history of leg ulcers was 2.4%, 18.6%, and 3.5% in SCD patients from the USA, Ghana, and Italy, respectively (Table 2). A minority of patients (4.3%, $N = 3$) with leg ulcers were taking hydroxyurea at the time of enrollment (Table 1). Conversely, only 2 out of the 59 adult patients (> 18 years old) on hydroxyurea developed leg ulcers (data not shown). The majority of leg ulcers occurred in adult SCD patients (14.9% vs. 2.9%, $p < 0.001$) and among the more severe sickle cell genotypes, hemoglobin SS and sickle beta thalassemia zero (13% vs. ≤ 3%, $p < 0.001$) (Table 2). Of note, the 7 pediatric patients who reported a history of leg ulcers were all from the Ghanaian site with a mean age of 9.5 (5.8 ± sd) years; 6 were SS genotype and 71% were male (data not shown).

The mean age of patients with a history of leg ulcer was 29.7(12.2 ± sd) years. Demographically, leg ulcer patients were more likely to be male ($p = 0.010$) and from the Ghanaian site (87%, $N = 59$ vs. 13%,$N = 9$, from the USA/Italy, $p < 0.001$) (Table 2). Clinically, patients with a history of leg ulcers had a lower oxygen saturation (94.3% vs. 97.0%, $p < 0.001$) and lower BMI (20 vs. 22.9, $p < 0.001$) (Table 3).

Table 1 Sociodemographic characteristics of study participants

	$N = 659$
Participants	*N* (%)
Country of residence	
USA	255 (38.7)
Ghana	318 (48.3)
Italy	86 (13.0)
Age group(years)	N (%)
Pediatric (< 18 years)	240 (36.4)
Mean age (range, sd)	9.6 (1–17, 4.5)
Adult (≥ 18 years old)	419 (63.6)
Mean age (range, sd)	29.9 (18–73.9, 11.2)
Gender	N (%)
Male	303 (46)
Female	356 (54)
Sickle cell genotype	N (%)
SS	474 (75)
SC	168 (19.2)
S Beta Thal +	29 (3.3)
S Beta Thal Zero	22 (2.5)
History of leg ulcer	N (%)
Yes	68 (10.3)
No	591 (89.7)
Hydroxyurea use	N(%)
Leg ulcer = yes	3 (4.3)
Leg ulcer = no	65 (95.7)

Hematological features of the study participants

SCD patients with a history of leg ulcers were more anemic (hemoglobin 7.5 g/dL vs. 9.1 g/dL, $p < 0.001$), had increased hemolysis (total bilirubin: Bili 3.6 mg/dl vs. 2.4 mg/dl, $p = 0.036$), and demonstrated higher leukocyte (12,900 vs. 10,400/ul) and platelet counts (438,000/ul vs. 367,000/ul, $p = 0.004$) (Table 3). Patients with a history of leg ulcers had greater microalbuminuria (UMA), proteinuria, and urine acidosis (UMA 112 mg/g vs. 59 mg/g $p = 0.015$; urine protein/creatinine 0.55 vs. 0.32, $p = 0.024$; urine pH = 5.6 vs. 5.9, $p = 0.008$) (Table 3). There was no significant relationship between a history of leg ulcers and frequency of pain crises requiring healthcare utilization or a history of stroke, avascular necrosis, or priapism (Table 3).

Subanalysis of leg ulcers of Ghanaian patients (Table 4)

The duration and onset of leg ulcers are described in Table 4, representing a subset of Ghanaian SCD patients that included 4 subcategorized age groups (< 21 years old, 21–30 years old, 31–40 years old, > 40 years old). The mean duration of leg ulcers was 4.6 years for the 48 patients who responded to this question; the longest mean duration, 7.25 years, was reported within the 31–40-year-old subgroup. The youngest subgroup (< 21 years old) described the shortest duration—mean 3.40 years—followed by the 21–30-year-old subgroup with

Table 2 Demographics of patients with leg ulcer and those without leg ulcer

	Leg ulcer		*p value
	Yes ($N = 68$)	No ($N = 591$)	
Country of residence	N (%)	N (%)	
USA	6 (2.4%)	249 (97.6%)	< 0.001**
**Ghana (87%of leg ulcer cases)	59 (18.6%)	259 (81.4%)	
Italy	3 (3.5%)	83 (96.5%)	
Genotype			
***SS	62 (13.0)	412 (87.0)	< 0.001***
SC	3 (2.3)	129 (97.7)	
SBeta Thal Zero	3 (13.0)	20 (87.0)	
SBeta Thal Plus	0 (0)	30 (100)	
Sex			
Male	42 (13.9)	261 (6.1)	0.010
Female	26 (7.4)	330 (92.6)	
Age category			
Pediatrics (< 18 years old)	7 (2.9)	233(97.1)	< 0.001
Adults (≥ 18 years old)	61(14.5)	358 (85.5)	

*p value, one way Anova for each category; **p value, Ghana vs. other countries;***p value, SS genotype vs. other genotypes; *p value < 0.05 was significant

a mean of 3.44 years. The oldest subgroup (> 40 years old) reported a mean leg ulcer duration of 5.8 years.

The mean age of onset of leg ulcers was 17.88 years within the Ghanaian subset. The earliest age at presentation was a mean of 9.33 years. The 21–30-year old and 31–40-year-old subgroups reported similar ages of onset, 17.54 years and 19.57 years, respectively. In the oldest subgroup, 24 years was the mean age of onset of leg ulcers.

Discussion

In this study, we observed that the majority of leg ulcers occurred in adult male patients with a severe SCD genotype from the Ghanaian CASiRe site. Our reported leg ulcer prevalence of 18.6% (59/318) in this subgroup of patients is higher than previous work from Ghana published by Ankra-Badu [18, 19]. The prevalence of leg ulcers in SCD patients has

Table 3 Clinical and hematological parameters of participants

	Leg ulcer		*p value
	Yes	No	
Clinical parameters			
Age mean, sd (N)	29.7 + 12.2 (68)	21.70 = +13.48 (51)	< 0.001
*BMI, mean, sd(N)	20 ± 3.6 (38)	22.9 ± 4.9 (232)	< 0.001
*Adults only			
Oxygen saturation, mean, %,sd (N)	94.3 ± 3.0 (22)	97.0 ± 2.8 (414)	< 0.001
Pain crises-E.R./day hospital/clinic visit/year	2.0 ± 3.1 (61)	1.61 + 3.1 (561)	0.269
Pain crises-hospitalizations year	1.1 ± 2.1 (64)	1.46 + 2.7 (565)	0.412
Laboratory studies			
WBC (1000/ul) mean, sd, (N)	12.7 ± 5.2 (63)	10.4 ± 4.3 (529)	< 0.001
Hemoglobin (g/dl) mean, sd,(N)	7.5 ± 1.8 (63)	9.1 ± 1.9 (528)	< 0.001
Platelet (1000/ul) mean, sd,(N)	465 ± 194 (60)	363 ± 164 (520)	< 0.001
Total bilirubin(mg/dl)mean, sd,(N)	3.8 ± 2.2 (9)	2.4 ± 1.7 (249)	0.017
Creatinine(mg/dl) mean, sd(N)	0.82 ± .31 (9)	0.52 ± .27 (264)	0.002
UMA (mg/g crt) mean, sd(N)	112 ± 182 (51)	59 ± 139 (356)	0.015
Urine protein/Crt mean, sd(N)	0.55 ± 0.70 (17)	0.32 ± 0.36 (215)	0.024
Urine pH mean, sd(N)	5.6 ± .59 (50)	5.9 ± .81 (360)	0.008
Urine specific gravity, mean, sd(N)	1.013 ± .03 (50)	1.015 ± 0.005 (360)	0.001

*p value: one way Anova for leg ulcer, yes vs. no; p value < 0.05 was significant; sd, standard deviation

Table 4 Subanalysis of Ghanaian SCD subjects with leg ulcers

Subgroups with leg ulcers ($N = 49$)		
Number of years with leg ulcers	Years (mean, sd)	N
All patients	4.64 ± 4.1	48
< 21 y/o	3.40 ± 3.0	5
21–30 y/o	3.44 ± 2.6	26
31–40 y/o	7.25 ± 2.6	12
> 40 y/o	5.80 ± 4.3	5
Leg ulcer age of onset (years)	Years (mean, sd)	N
All patients	17.80 ± 7.9	49
<21 y/o	9.33 ± 5.0	6
21–30 y/o	17.54 ± 5.4	24
31–40 y/o	19.57 ± 6.5	14
> 40 y/o	24.20 ± 15.4	5

y/o, years/old; sd, standard deviation

been reported to vary from country to country due to a number of factors including age, gender, and SCD genotype [6]. Previous studies in Jamaica recorded a prevalence of leg ulcers of 75%; in North America, the prevalence was 1–10% of SCD patients [17, 20, 21]. Additional single center studies conducted in northwest Nigeria, Sierra-Leone, and Ghana have reported a wide range in leg ulcer prevalence, 3.1% to 13.2% [9, 15, 22, 23]. The Cooperative Study of Sickle Cell Disease (CSSCD) in the USA reported a leg ulcer prevalence of 2.5% in persons above 10 years of age [12], which is similar to the 2.4% recorded among US SCD patients in our study. A study conducted in Jamaica reported SCD patients above the age of 18 years have the highest risk of developing leg ulcers [13], supporting our findings of an adult predominance (14.5% vs. 2.9% in pediatric patients). This indeed suggests a correlation between ages as it relates to SCD pathophysiology and leg ulcer development. Finally, more than 75% of the global burden of SCD exists in sub-Saharan Africa [2]. Thus, it is not surprising that we noted a higher prevalence of leg ulcers among the adult Ghanaian SCD patients as compared with those from the USA and Italy in our CASiRe cohort.

Leg ulcers are one of the most devastating clinical complications in SCD, particularly in patients with the SS genotype [5, 12]. The majority of studies to date have reported a higher frequency of leg ulcers within the more severe SCD genotypes as compared with the less severe genotypes, i.e., SC [6, 12, 19]. In our CASiRe cohort, the prevalence of leg ulcers in SS patients (13%) was greater than 5 times that of their SC counterparts (2.3%). A retrospective study of over 500 US SCD patients documented a history of leg ulcers in 22% with the SS genotype but only 9% with the SC genotype, primarily among adults [24]. The significant, chronic hemolysis associated with SCD, particularly the SS genotype, is likely playing a large role in the development of leg ulcers and could be the underlying mechanism contributing to the difference in incidence observed between the genotypes [24, 25]. Previous studies have reported leg ulcers were associated with the most severe degree of hemolysis, which was most characterized by lower hemoglobin levels and elevated markers of hemolysis (lactate dehydrogenase levels (LDH), aspartate aminotransferase (AST), total bilirubin (TBili)) [10, 11, 13, 26]. Minniti et al. reported significantly lower hemoglobin levels and higher hemolytic markers in US patients with leg ulcers, including higher LDH, AST, and absolute reticulocyte counts. The results from our study are consistent with these findings. Lower hemoglobin level had the strongest correlation ($p < 0.001$) to leg ulcers compared with TBili ($p = 0.017$) among markers of hemolysis within our CASiRe SCD cohort.

Hypoxemia, as measured by lower oxygen saturation levels, has also been linked to higher hemolysis in multiple studies [26–28]. Leg ulcer patients within our CASiRe cohort had significantly lower mean oxygen saturation further supporting the association with hemolysis. We propose that the degree of hemolysis in SCD patients could influence the development of leg ulcers.

The relationship between hydroxyurea and leg ulcers is fraught with controversy. While several anecdotal studies have reported that the use of hydroxyurea may exacerbate, or cause, leg ulcers [29, 30], this has not been demonstrated in large well-controlled studies [6]. In addition, there is little data to suggest that hydroxyurea can improve leg ulcers as part of a specific treatment strategy [6]. In our cohort, less than 10% of leg ulcer patients were on hydroxyurea, so we cannot conclusively determine the effects of hydroxyurea on the treatment of leg ulcers. However, our study does show that patients who were taking hydroxyurea to prevent other complications of the disease were less likely to develop leg ulcers; only three out of 59 (5%) of our patients on hydroxyurea developed leg ulcers. This may be related to increased rheology, reduced hemolysis, and increased life span of the red cells. Enhanced vascular tone due to nitric oxide donation or improvement of vasculopathy and adhesion, as noted by decreased white blood cell and platelet counts, may also be important.

As a sign of chronic disease, leg ulcers typically develop in late adolescence to young adulthood [31]. Many times, patients who develop leg ulcers go on to develop chronic or recurrent leg ulcers [21]. Approximately 25% of patients can develop small recurrent ulcers [21]; often it is hard to distinguish between a new ulcer and previously healed, recurrent ulcer [6, 21]. Our data show that patients can present with leg ulcers as early as 9 years of age. Most leg ulcers have remained for at least 3 years and some as long as 7 years.

Additionally, clinical complications including acute chest syndrome, thrombosis, renal disease, and elevated tricuspid jet regurgitation have been linked to leg ulcers [24, 32, 33]. Renal disease appears to be a predominant complication within the

CASiRe leg ulcer cohort. Significantly elevated mean urine microalbumin and protein/creatinine levels were found within our leg ulcer patients. Acidosis and hyposthenuria were additional markers of renal dysfunction observed in our leg ulcer patients. Lastly, we did not find any association of the frequency of painful crises and leg ulcers as measured by visits to the emergency room/clinic/day hospital or hospitalizations.

The high prevalence of leg ulcers in Ghana may be a result of other factors including the warm tropical climate, as well as high humidity, which may favor persistence of skin lesions. Moreover, Ghana is a developing country, and, as such, there may be a limited availability of health services leading to delayed presentation and treatment. The cost of healthcare services could also be a limiting factor in patients seeking care, resulting in increased severity and/or recurrence of leg ulcers [34]. Ghanaian SCD patients with small open wounds in the lower legs may not seek prompt medical care resulting in possible development of leg ulceration. In fact, antecedent trauma was present in 40% of Ghanaian SCD patients with leg ulcers in one report [18].

In line with many other studies, the frequency of leg ulcers in our cohort was observed to be higher among male SCD patients [12, 15, 18, 19, 35]. Some studies, however, have also reported no association between gender and leg ulcer development [6, 17, 36]. This finding warrants additional investigation.

Conclusion

This study presents a comprehensive analysis of leg ulcer prevalence, SCD demographics, and clinical risk factors within a cohort of international SCD patients. Multiple factors contribute to the development of leg ulcers; West African background, male gender, and age were associated demographic risk factors for leg ulcers in our cohort. Associated leukocytosis and thrombocytosis suggest increased adhesion within the vessel bed as a contributing factor to leg ulcer development. Further, severe anemia, lower oxygen saturation, and evidence of brisk hemolysis (elevated TBili, lower hemoglobin) support previous findings of the role of chronic hemolysis in the development of this morbid complication. Hydroxyurea was not associated with leg ulcers. Renal acidosis, albuminuria, and proteinuria support its possible association with renal dysfunction. Further studies are needed in a larger cohort to validate these findings.

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Compliance with ethical standards

Conflict of interest **A Campbell**: Research Funding from Global Blood Therapeutics, Novartis, Cyclerion; Consultancy for Global Blood Therapeutics, Cyclerion and Bluebird Bio; **D Manwani:** Research funding from Grifols; Consultancy for Novartis, Pfizer, Blood Therapeutics; **B Andemariam:** Consultancy for Novartis, Pfizer, NovoNordisk, Emmaus, Cyclerion, Terumo, Sanofi; DSMB: Global Blood Therapeutics; Research Funding: Imara; **B Inusa:** Education Funding: Novartis Ast raZeneca, Global Blood Therapeutics, Celgene, Vertex; **C. Strunk**: Consultancy Global Blood Therapeutics and Novartis; **C Piccone**: Consultancy for Global Blood Therapeutics and Novartis; **R Colombatti:** Research Funding: Global Blood Therapeutics, Novartis.

Ethical approval With the exception of Azienda Ospedaliera-Università di Padova, where there was a previously IRB-approved SCD Registry, IRB approval was obtained at all sites, and written informed consent was obtained from each patient and/or parent/guardian. Ethical approval for the study was sought from the Ethical and Protocol Review Committee of each participating site.

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